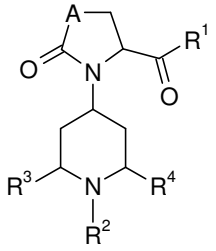
context) endothelial cells of the retinal vasculature, and studies on rodents have shown promise in alleviating retinal disease-associated neovascularization.

[0009] Despite this promise, there has been a failure in the industry to develop a CCR3 antagonist for human treatment of retina-associated disease. However, the compounds, co-crystals, salts, and formulations disclosed herein, which specifically modulate/antagonize CCR3, are effective at improving the visual acuity of a significant number of subjects, even while effects on neovascularization are insignificant.

SUMMARY

[0010] In a first aspect, the present disclosure refers to the use of a compound of formula 1,



Formula 1 as defined in claim 1 in the manufacture of a medicament for improving visual acuity in a subject diagnosed with a retina-associated disease. Also described herein are methods of treating patients for retinal-associated diseases are provided, including dry and wet age-associated macular degeneration, central retinal vein occlusion, retinopathy of prematurity, and diabetic retinopathy. A method of improving visual acuity in a subject (such as a subject diagnosed with a retina-associated disease) is provided. Examples of the methods include modulation of CCR3, the principal receptor of CCL11/eotaxin-1 through the administration of an effective amount of CCR3 antagonists of the invention. The methods include administering effective therapeutic doses of CCR3 antagonists (e.g., a compound of Formula 1 described herein) to subjects or patients as well as monitoring for specific clinical endpoints.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] **Figure 1** is a table of potency and species selectivity for an investigational product of the invention.

[0012] **Figure 2** depicts the overall clinical trial design and plan using the investigational product of the invention including screening, treatment, and follow-up periods.

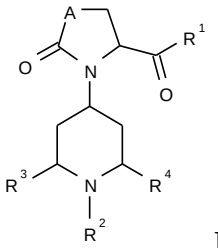
[0013] **Figure 3** depicts mean central 1-mm retinal thickness in patients over the clinical trial timeline described in Figure 2.

[0014] **Figure 4** is a table of descriptive statistics with respect to neovascular leakage over the clinical trial timeline described in Figure 2.

[0015] **Figure 5** depicts best-corrected visual acuity (BCVA) by number of letters read by patients over the time of trial described in Figure 2. BCVA was tested using the ETDRS chart for visual acuity.

What is claimed:

1. Use of a compound of formula 1,



Formula 1

wherein

A is CH_2, O or N-C_{1-6}-alkyl;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-C_{3-6}-cycloalkyl, whereas optionally one carbon atom is replaced by a nitrogen atom, whereas the ring is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, O-C_{1-6}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen, CN, SO_2-C_{1-6}-alkyl, COO-C_{1-6}-alkyl;
- a $C_{9 \text{ or } 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by nitrogen atoms and the ring system is bound via a nitrogen atom to the basic structure of formula **1** and whereas the ring system is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, COO-C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, NO_2, halogen, CN, $NHSO_2$-C_{1-6}-alkyl, methoxy-phenyl;
- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-6}-alkyl, NHCH(CH_2O-C_{1-6}-alkyl)-benzoimidazolyl, optionally substituted with halogen or CN;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazole;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-haloalkyl, C_{1-6}-alkylene-OH, C_{2-6}-alkenylene-OH, C_{2-6}-alkynylene-OH, $CH_2CON(C_{1-6}\text{-alkyl})_2$, $CH_2NHCONH$-C_{3-6}-cycloalkyl, CN, CO-pyridinyl, $CONR^{1.1.1}R^{1.1.2}$,

$COO\text{-}C_{1\text{-}6}$-alkyl, $N(SO_2\text{-}C_{1\text{-}6}\text{-alkyl})(CH_2CON(C_{1\text{-}4}\text{-alkyl})_2)$ $O\text{-}C_{1\text{-}6}$-alkyl, O-pyridinyl, $SO_2\text{-}C_{1\text{-}6}$-alkyl, $SO_2\text{-}C_{1\text{-}6}$-alkylen-OH, $SO_2\text{-}C_{3\text{-}6}$-cycloalkyl, SO_2-piperidinyl, $SO_2NH\text{-}C_{1\text{-}6}$-alkyl, $SO_2N(C_{1\text{-}6}\text{-alkyl})_2$, halogen, CN, CO-morpholinyl, CH_2-pyridinyl or a heterocyclic ring optionally substituted with one or two residues selected from the group consisting of $C_{1\text{-}6}$-alkyl, $NHC_{1\text{-}6}$-alkyl and =O;

$R^{1.1.1}$ is selected from H, $C_{1\text{-}6}$-alkyl, $C_{3\text{-}6}$-cycloalkyl, $C_{1\text{-}6}$-haloalkyl, $CH_2CON(C_{1\text{-}6}\text{-alkyl},)_2$, CH_2CO-azetindinyl, $C_{1\text{-}6}$-alkylen-$C_{3\text{-}6}$-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, $C_{1\text{-}6}$-alkylen-OH or thiadiazolyl, optionally substituted is selected from with $C_{1\text{-}6}$-alkyl;

$R^{1.1.2}$ H, $C_{1\text{-}6}$-alkyl, $SO_2C_{1\text{-}6}$-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one N or O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of $C_{1\text{-}6}$-alkyl, $C_{1\text{-}4}$-alkylene-OH, OH, =O;

or

$R^{1.1}$ is phenyl, wherein two adjacent residues are together forming a five- or six-membered carbocyclic aromatic or non-aromatic ring, optionally containing independently from each other one or two N, S, or SO_2, replacing a carbon atom of the ring, wherein the ring is optionally substituted with $C_{1\text{-}4}$-alkyl or =O;

$R^{1.2}$ is selected from

- heteroaryl, optionally substituted with one or two residues selected from the group consisting of $C_{1\text{-}6}$-alkyl, $C_{2\text{-}6}$-alkenyl, $C_{2\text{-}6}$-alkynyl, $C_{3\text{-}6}$-cycloalkyl, $CH_2COO\text{-}C_{1\text{-}6}$-alkyl, $CONR^{1.2.1}R^{1.2.2}$, $COR^{1.2.3}$, $COO\text{-}C_{1\text{-}6}$-alkyl, $CONH_2$, $O\text{-}C_{1\text{-}6}$-alkyl, halogen, CN, $SO_2N(C_{1\text{-}6}\text{-alkyl})_2$ or heteroaryl optionally substituted with one or two residues selected from the group consisting of $C_{1\text{-}6}$-alkyl;
- heteroaryl, optionally substituted with a five- or six-membered carbocyclic non-aromatic ring containing independently from each other two N, O, S, or SO_2, replacing a carbon atom of the ring;

- an aromatic or non-aromatic $C_{9 \text{ or } 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by N, O or S each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-6}\text{-alkyl})_2$, CONH-$C_{1-6}$-alkyl, =O;
- a heterocyclic non-aromatic ring, optionally substituted with pyridinyl; or
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCO-C_{1-6}-alkyl;

$R^{1.2.1}$ is selected from H, C_{1-6}-alkyl, C_{1-6}-alkylene-C_{3-6}-cycloalkyl, C_{1-4}-alkylene-phenyl, C_{1-4}-alkylene-furanyl, C_{3-6}-cycloalkyl, C_{1-4}-alkylene-O-C_{1-4}-alkyl, C_{1-6}-haloalkyl or a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring, optionally substituted with 4-cyclopropylmethyl-piperazinyl

$R^{1.2.2}$ is selected from H, C_{1-6}-alkyl;

$R^{1.2.3}$ is selected from a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring;

$R^{1.3}$ is selected from phenyl, heteroaryl or indolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, phenyl, heteroaryl;

R^2 is selected from the group consisting of C_{1-6}-alkylene-phenyl, C_{1-6}-alkylene-naphthyl, and C_{1-6}-alkylene-heteroaryl; each optionally substituted with one, two or three residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, halogen;

R^3 is selected from H, or C_{1-6}-alkyl;

R^4 is selected from H, or C_{1-6}-alkyl;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group;

in the manufacture of a medicament for improving visual acuity in a subject diagnosed with a retina-associated disease.

2. The use of claim 1 wherein the retina-associated disease is from the group consisting of dry age-related macular degeneration, wet age-related macular degeneration, central retinal vein occlusion, retinopathy of prematurity, and diabetic retinopathy.

3. The use of claim 1 or 2 wherein the compound of formula 1, wherein

A is CH_2, O or N-C_{1-4}-alkyl;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-C_{3-6}-cycloalkyl, whereas optionally one carbon atom is replaced by a nitrogen atom, whereas the ring is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, O-C_{1-6}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen, CN, SO_2-C_{1-6}-alkyl, COO-C_{1-6}-alkyl;
- a $C_{9 \text{ or } 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by nitrogen atoms and the ring system is bound via a nitrogen atom to the basic structure of formula **1** and whereas the ring system is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, COO-C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, NO_2, halogen, CN, $NHSO_2$-C_{1-6}-alkyl, m-methoxyphenyl;
- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-6}-alkyl, NHCH(CH_2O-C_{1-6}-alkyl)-benzoimidazolyl, optionally substituted with Cl;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazolyl;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl})_2$, $CH_2NHCONH$-C_{3-6}-cycloalkyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, SO_2-C_{1-6}-alkyl, SO_2-C_{1-6}-alkylen-OH, SO_2-C_{3-6}-cycloalkyl, SO_2-piperidinyl, SO_2NH-C_{1-6}-alkyl, $SO_2N(C_{1-6}\text{-alkyl})_2$, halogen, CN, CO-morpholinyl, CH_2-pyridinyl or a heterocyclic ring optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, NHC_{1-6}-alkyl, =O;

$R^{1.1.1}$ is selected from H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl},)_2$, CH_2CO-azetindinyl,

C_{1-6}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, C_{1-6}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-6}-alkyl;

$R^{1.1.2}$ is selected from H, C_{1-6}-alkyl, or SO_2C_{1-6}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH

$R^{1.2}$ is selected from

- heteroaryl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, CH_2COO-C_{1-6}-alkyl, $CONR^{1.2.1}R^{1.2.2}$, COO-C_{1-6}-alkyl, $CONH_2$, O-C_{1-6}-alkyl, halogen, CN, CO-pyrrolidinyl, CO-morpholinyl or heteroaryl optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl;
- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-6}\text{-alkyl})_2$, $CONH$-C_{1-6}-alkyl, =O;
- piperidinyl, optionally substituted with pyridinyl; or
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with $NHCO$-C_{1-6}-alkyl, wherein

  $R^{1.2.1}$ is H, or C_{1-6}-alkyl;

  $R^{1.2.2}$ is H, or C_{1-6}-alkyl;

$R^{1.3}$ is selected from phenyl, pyrazolyl, isoxazolyl, pyrimidinyl, indolyl or oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, halogen; or CH_2-thiophenyl, optionally substituted with one or two residues selected from the group consisting of halogen;

R^3 is H, or C_{1-4}-alkyl;

R^4 is H, or C_{1-4}-alkyl;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

4. The use of claim 1 or 2 ,wherein the compound of formula 1 is

A is CH_2, O or NMe;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-cyclohexyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen;
- NH-pyrrolidinyl, optionally substituted with one or two residues selected from the group consisting of SO_2-C_{1-4}-alkyl, COO-C_{1-4}-alkyl;
- piperidinyl, optionally substituted with one or two residues selected from the group consisting of $NHSO_2$-C_{1-4}-alkyl, m-methoxyphenyl;
- dihydro-indolyl, dihydro-isoindolyl, tetrahydro-quinolinyl or tetrahydro-isoquinolinyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, COO-C_{1-4}-alkyl, C_{1-4}-haloalkyl, O-C_{1-4}-alkyl, NO_2, halogen;
- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-4}-alkyl, NHCH(CH_2O-C_{1-4}-alkyl)-benzoimidazolyl, optionally substituted with Cl;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazolyl; wherein

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{1-4}-haloalkyl, $CH_2CON(C_{1-4}\text{-alkyl})_2$, $CH_2NHCONH$-C_{3-6}-cycloalkyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COO-C_{1-4}-alkyl, O-C_{1-4}-alkyl, SO_2-C_{1-4}-alkyl, SO_2-C_{1-4}-alkylen-OH, SO_2-C_{3-6}-cycloalkyl, SO_2-piperidinyl, SO_2NH-C_{1-4}-alkyl, $SO_2N(C_{1-4}\text{-alkyl})_2$, halogen, CO-morpholinyl, CH_2-pyridinyl, or imidazolidinyl, piperidinyl, oxazinanyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrimidinyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, NHC_{1-4}-alkyl,, =O;

$R^{1.1.1}$ is selected from H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-haloalkyl, $CH_2CON(C_{1-4}\text{-alkyl},)_2$, CH_2CO-azetindinyl, C_{1-4}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl,

CH_2-furanyl, C_{1-4}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-4}-alkyl;

$R^{1.1.2}$ is selected from H, C_{1-4}-alkyl, SO_2C_{1-4}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH

$R^{1.2}$ is selected from

- pyridinyl, pyridazinyl, pyrrolyl, pyrazolyl, isoxazolyl, thiazolyl, thiadiazolyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, CH_2COO-C_{1-4}-alkyl, $CONR^{1.2.1}R^{1.2.2}$, COO-C_{1-4}-alkyl, $CONH_2$, O-C_{1-4}-alkyl, halogen, CO-pyrrolidinyl, CO-morpholinyl or pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl;
- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-4}\text{-alkyl})_2$, $CONH$-C_{1-4}-alkyl, =O;
- piperidinyl, optionally substituted with pyridinyl; or
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with $NHCO$-C_{1-4}-alkyl, wherein

  $R^{1.2.1}$ is H, or C_{1-4}-alkyl;

  $R^{1.2.2}$ is H, or C_{1-4}-alkyl;

$R^{1.3}$ is selected from phenyl, pyrazolyl, isoxazolyl, pyrimidinyl, indolyl or oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-4}-alkyl, O-C_{1-4}-haloalkyl;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{1-4}-haloalkyl, O-C_{1-4}-haloalkyl, halogen; or CH_2-thiophenyl, optionally substituted with one or two residues selected from the group consisting of halogen;

R^3 is H;

R^4 is H;

or **R**^{3} and **R**^{4} together are forming a CH_2-CH_2 group.

5. The use of claim 1 or 2, wherein formula 1 is

A is CH_2, O or NMe;

R^{1} is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-piperidinyl, optionally substituted with pyridinyl;
- NH-cyclohexyl, optionally substituted with one or two residues selected from the group consisting of t-Bu, $NHSO_2$-phenyl, NHCONH-phenyl, F;
- NH-pyrrolidinyl, optionally substituted with one or two residues selected from the group consisting of SO_2Me, COO-t-Bu;
- piperidinyl, optionally substituted with one or two residues selected from the group consisting of $NHSO_2$-n-Bu, m-methoxyphenyl;
- dihydro-indolyl, dihydro-isoindolyl, tetrahydro-quinolinyl or tetrahydro-isoquinolinyl, optionally substituted with one or two residues selected from the group consisting of Me, COOMe, CF_3, OMe, NO_2, F, Br;
- a group selected from NHCH(pyridinyl)CH_2COOMe, NHCH(CH_2OMe)-benzoimidazolyl, optionally substituted with Cl;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazolyl; wherein

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, t-Bu, CF_3, CH_2CONMe_2, CH_2NHCONH-cyclohexyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COOMe, COOEt, OMe, SO_2Me, $SO_2CH_2CH_2OH$, SO_2Et, SO_2-cyclopropyl, SO_2-piperidinyl, SO_2NHEt, SO_2NMeEt, F, Cl, CO-morpholinyl, CH_2-pyridinyl, or imidazolidinyl, piperidinyl, oxazinanyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrimidinyl, each optionally substituted with one or two residues selected from the group consisting of Me, NHMe, =O;

$R^{1.1.1}$ is selected from H, Me, Et, t-Bu, i-Pr, cyclopropyl, CH_2-i-Pr, CH_2-t-Bu, $CH(CH_3)CH_2CH_3$, CH_2CHF_2, CH_2CONMe_2, CH_2CO-azetindinyl, CH_2-cyclopropyl, CH_2-cyclobutyl, CH_2-pyranyl,

CH_2-tetrahydrofuranyl, CH_2-furanyl, CH_2CH_2OH or thiadiazolyl, optionally substituted with Me;

$R^{1.1.2}$ is selected from H, Me, Et, SO_2Me, or SO_2Et,

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH;

$R^{1.2}$ is selected from

- pyridinyl, pyrrolyl, pyrazolyl, isoxazolyl, thiazolyl, thiadiazolyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, Pr, Bu, cyclopropyl, CH_2COOEt, $CONR^{1.2.1}R^{1.2.2}$, COOMe, COOEt, $CONH_2$, OMe, Cl, Br CO-pyrrolidinyl, CO-morpholinyl or pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, each optionally substituted Me;
- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of NMe_2, CONHMe, =O;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCOMe, wherein

  $R^{1.2.1}$ is H, or Me;

  $R^{1.2.2}$ is H, or Me;

$R^{1.3}$ is selected from phenyl, pyrazolyl, isoxazolyl, pyrimidinyl, indolyl or oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of Me, Et, Pr, cyclopentyl, OMe, $OCHF_2$;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of CH_3, CF_3, OCF_3, F, Cl, Br, Et; or CH_2-thiophenyl, optionally substituted with one or two residues selected from the group consisting of Cl, Br;

R^3 is H;

R^4 is H;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

6. The use of claim 1 or 2, wherein formula 1 is

A is CH_2, O or NMe;

R^1 is selected from

- $NHR^{1.1}$
- $NHR^{1.2}$,

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, Bu, CF_3, CH_2CONMe_2, $CH_2NHCONH$-cyclohexyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COOMe, COOEt, OMe, SO_2Me, $SO_2CH_2CH_2OH$, SO_2Et, SO_2-cyclopropyl, SO_2-piperidinyl, SO_2NHEt, SO_2NMeEt, F, Cl, CO-morpholinyl, CH_2-pyridinyl, or imidazolidinyl, piperidinyl, oxazinanyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrimidinyl, each optionally substituted with one or two residues selected from the group consisting of Me, NHMe, =O; wherein

$R^{1.1.1}$ is selected from H, Me, Et, t-Bu, i-Pr, cyclopropyl, CH_2-i-Pr, CH_2-t-Bu, $CH(CH_3)CH_2CH_3$, CH_2CHF_2, CH_2CONMe_2, CH_2CO-azetindinyl, CH_2-cyclopropyl, CH_2-cyclobutyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, CH_2CH_2OH or thiadiazolyl, optionally substituted with Me;

$R^{1.1.2}$ is selected from H, Me, Et, SO_2Me, SO_2Et;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH

$R^{1.2}$ is selected from

- pyridinyl, pyrrolyl, pyrazolyl, isoxazolyl, thiazolyl, thiadiazolyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, Pr, Bu, cyclopropyl, CH_2COOEt, $CONR^{1.2.1}R^{1.2.2}$, COOMe, COOEt, $CONH_2$, OMe, Cl, Br CO-pyrrolidinyl, CO-morpholinyl or pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, each optionally substituted Me;

- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of NMe_2, CONHMe, =O;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCOMe, wherein

  $R^{1.2.1}$ is H, or Me;

  $R^{1.2.2}$ is H, or Me;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of CH_3, CF_3, OCF_3, F, Cl, Br, Et;

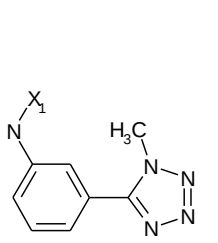
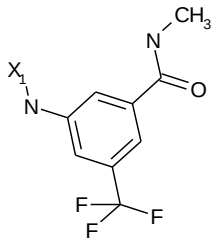
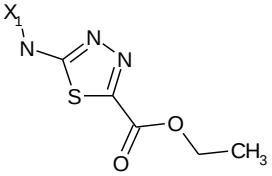
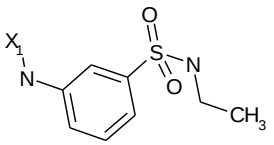
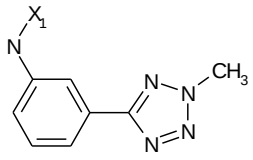
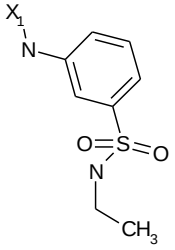
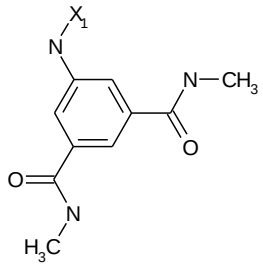
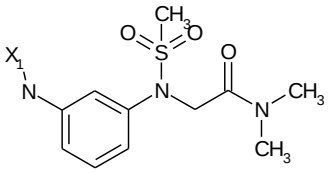
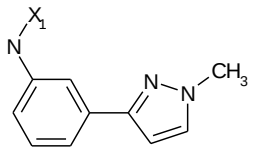
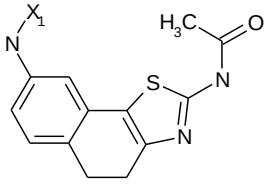
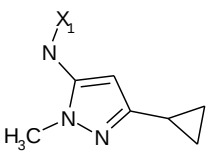
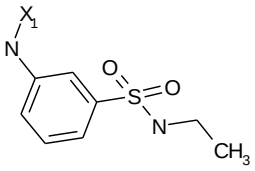
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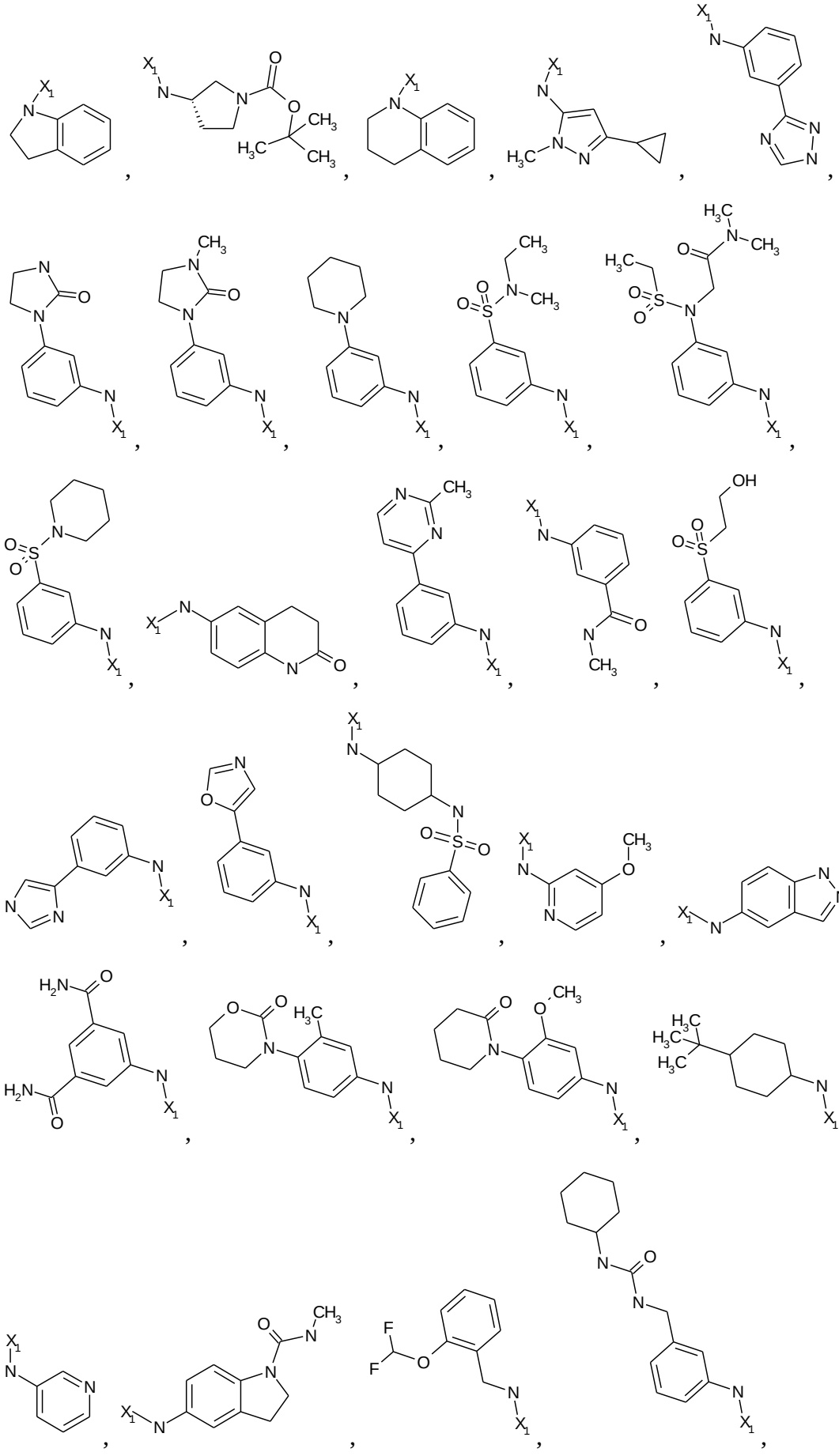
R^4 is H.

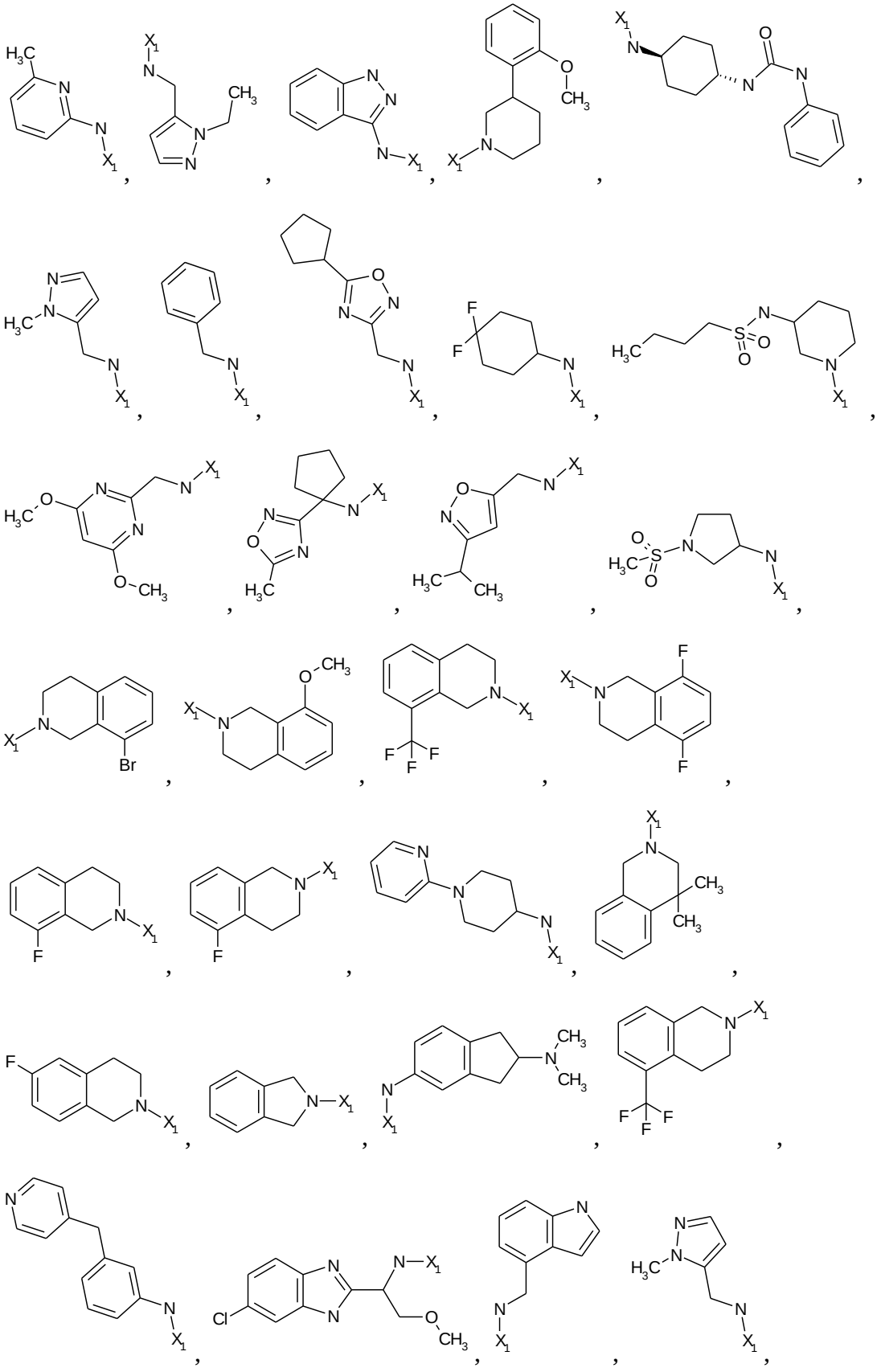
7. The use of claim 1 or 2, wherein formula 1 is

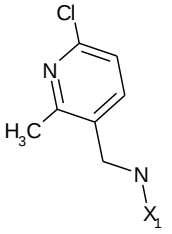
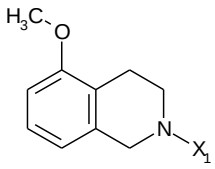
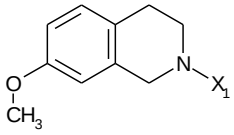
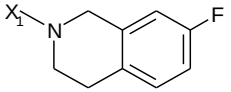
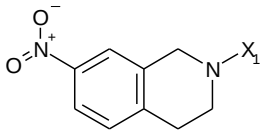
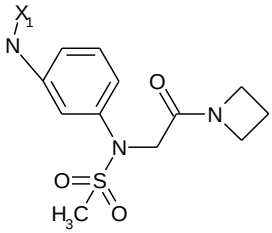
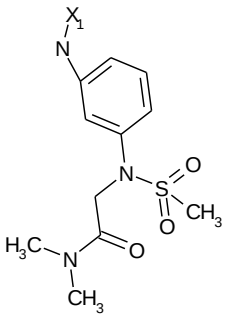
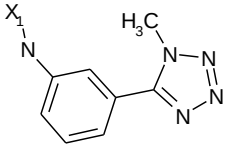
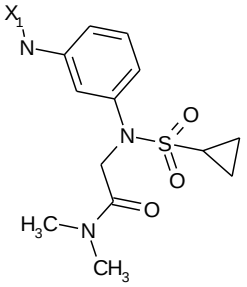
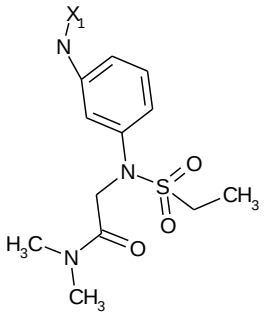
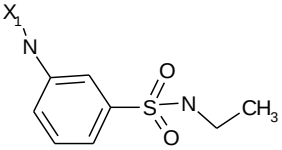
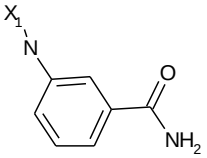
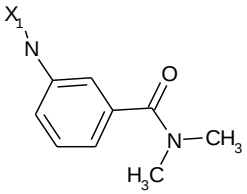
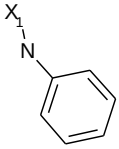
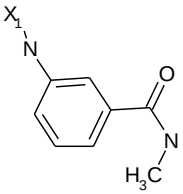
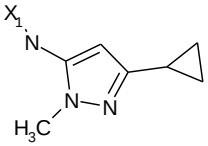
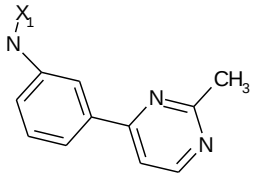
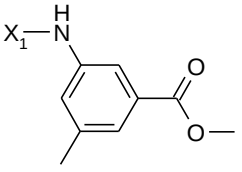
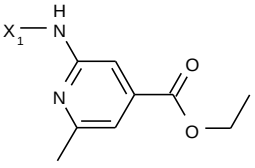
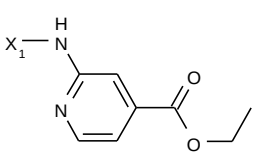
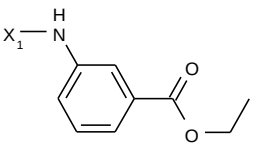
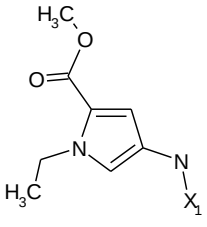
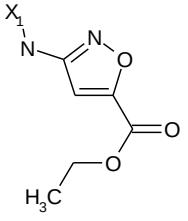
A is CH_2, O or NMe;

R^1 is selected from


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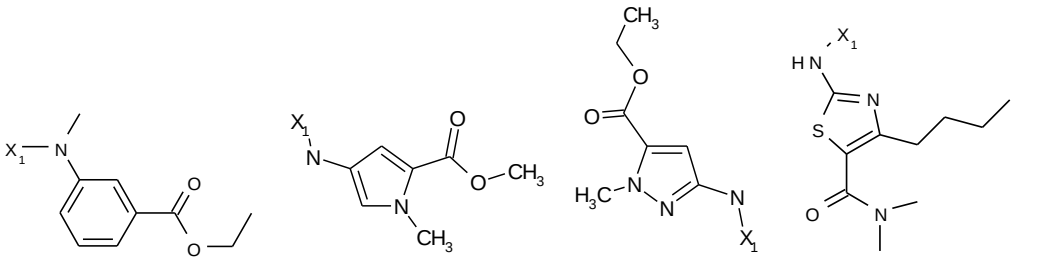

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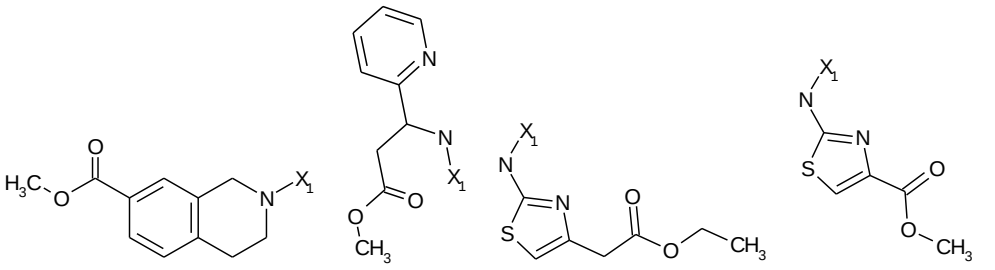
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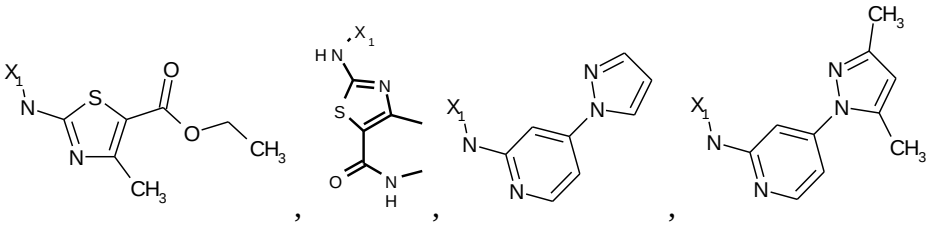
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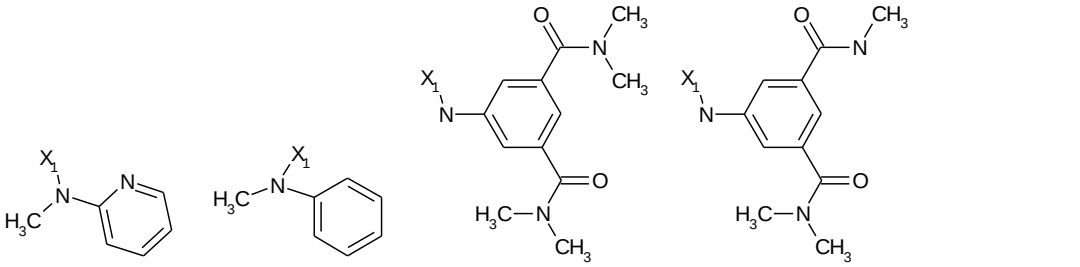
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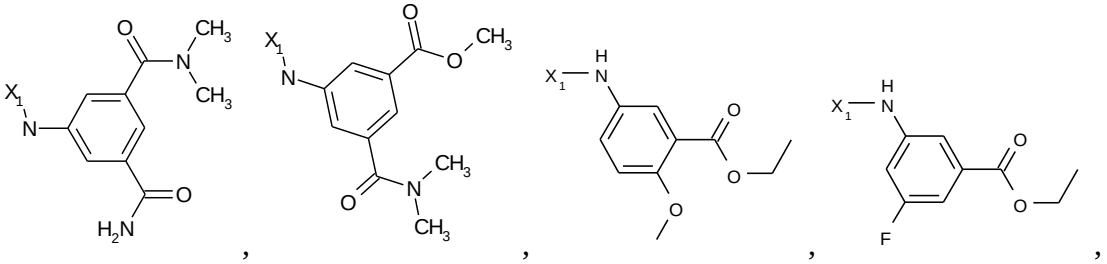
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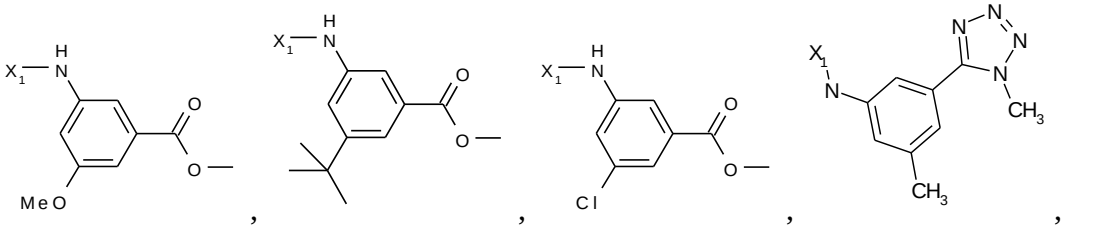


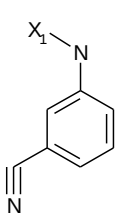
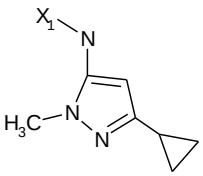
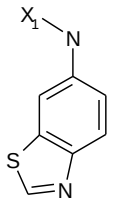
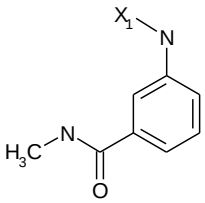
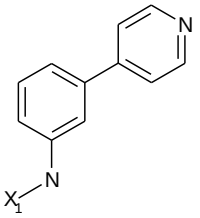
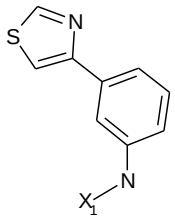
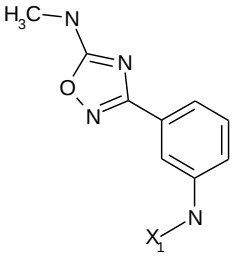
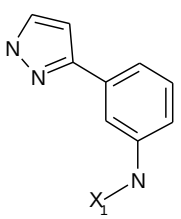
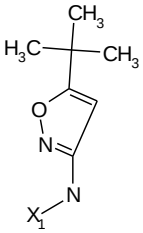
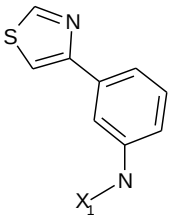
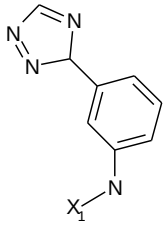
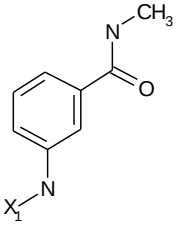
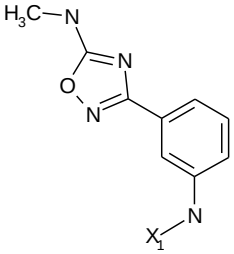
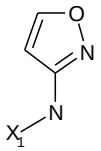
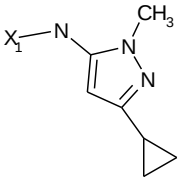
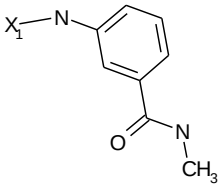
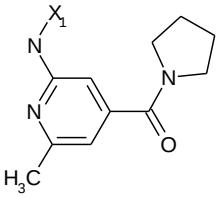
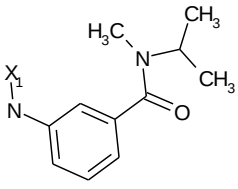
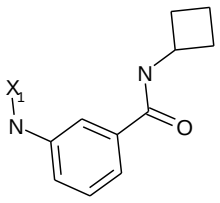
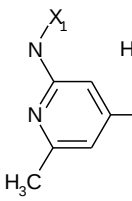


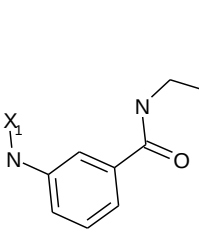
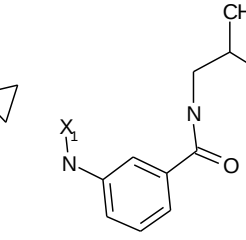
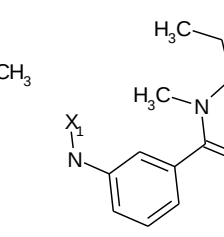









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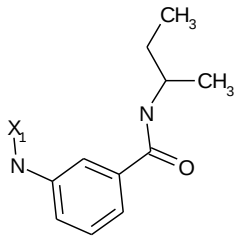
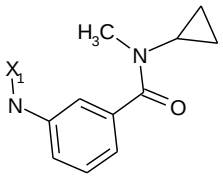
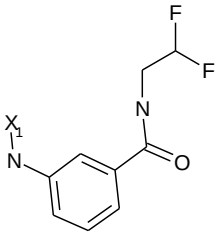
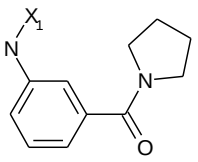
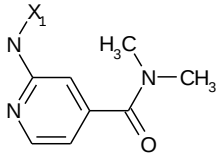
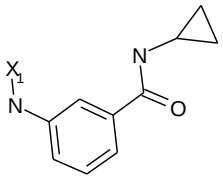
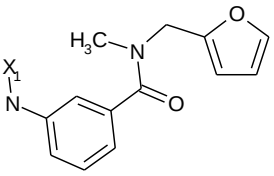
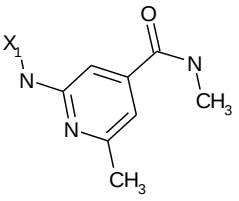
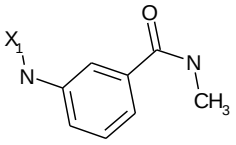
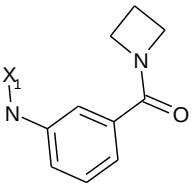
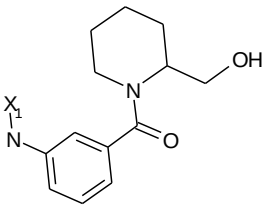
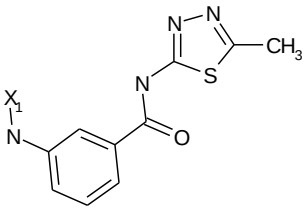
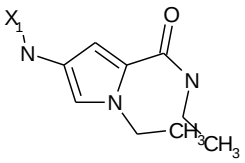
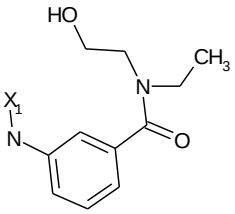
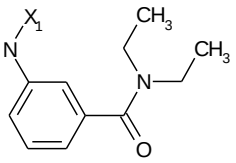
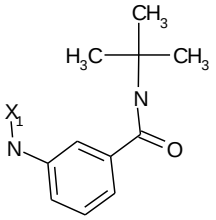
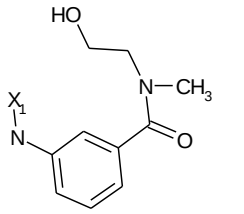
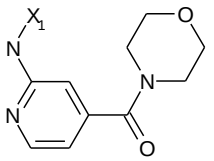
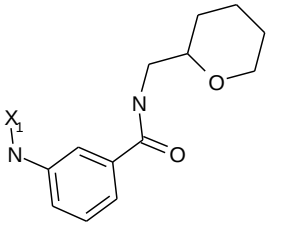
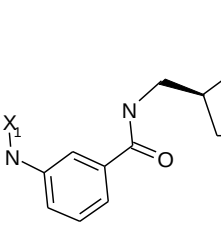
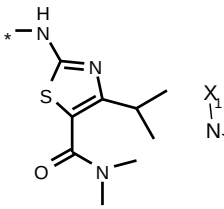
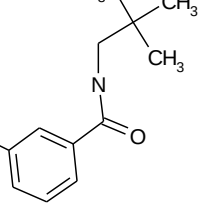
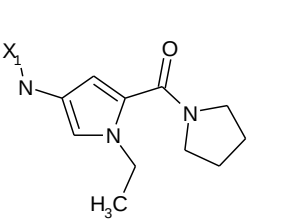
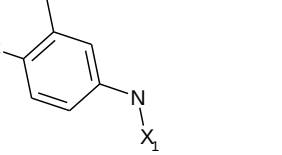
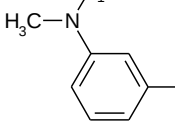
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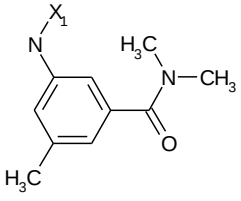
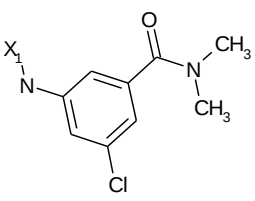
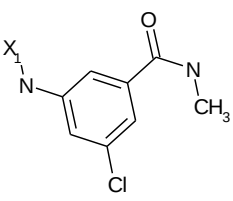
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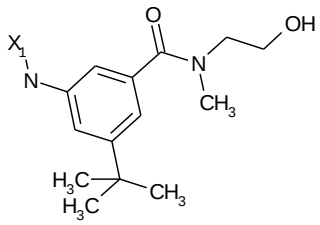
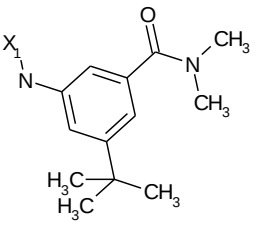
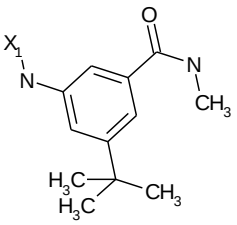
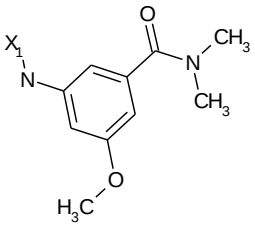
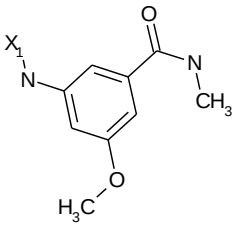
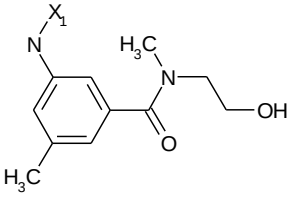
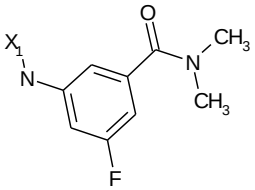
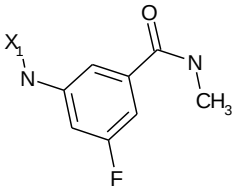
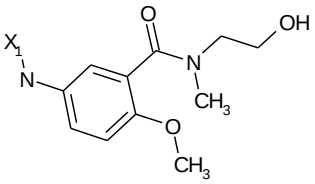
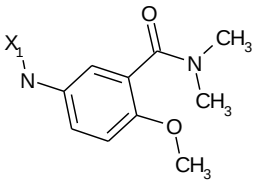
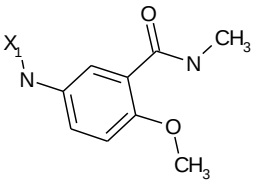
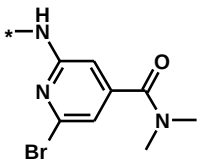
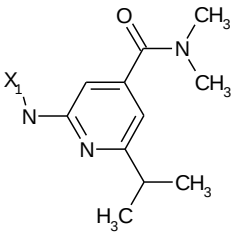
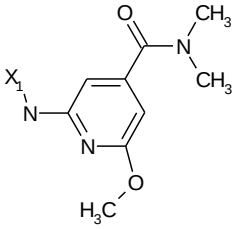
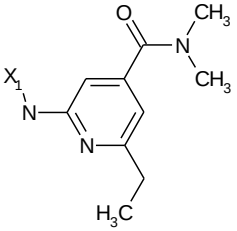
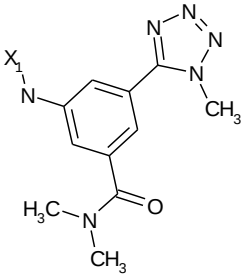
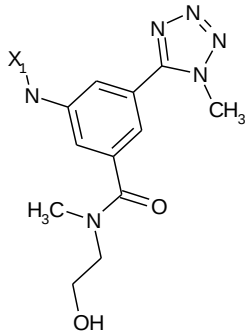
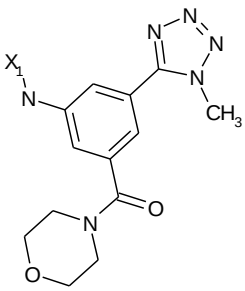
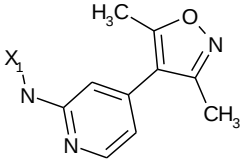
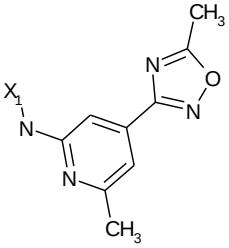
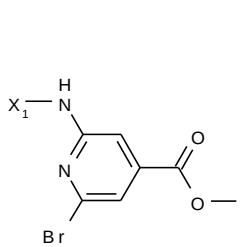

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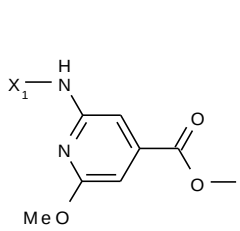
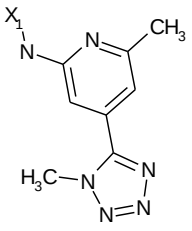
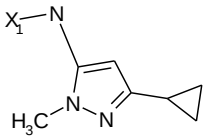
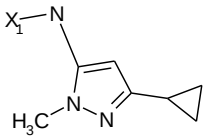
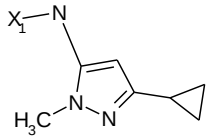
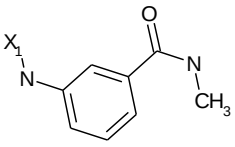
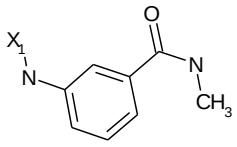
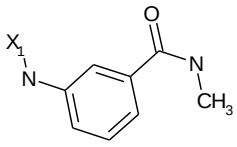
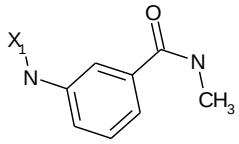
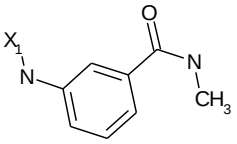
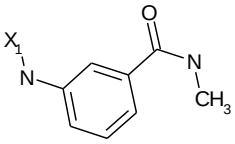
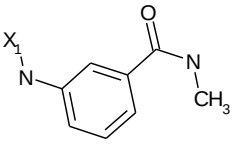
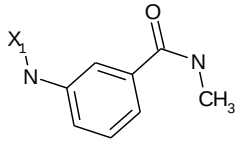
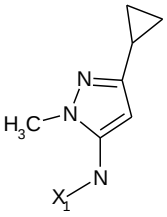
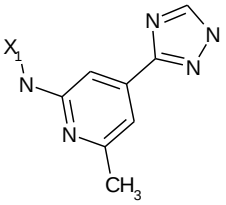
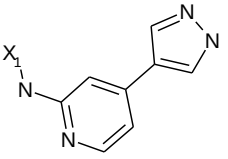
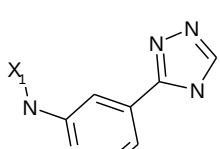
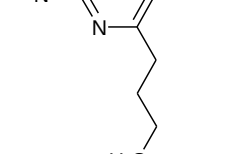
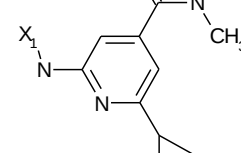
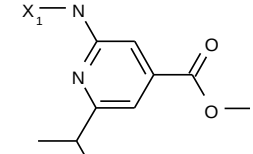
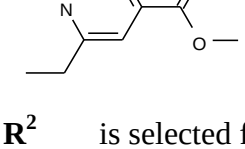

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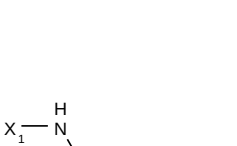
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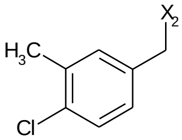
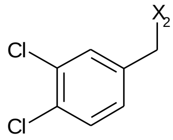
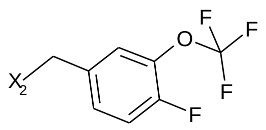
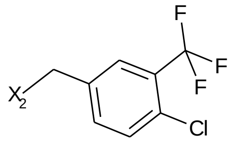

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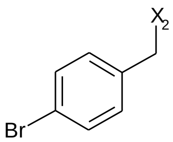
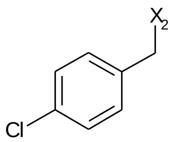
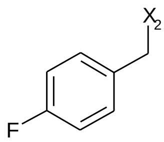
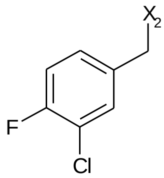
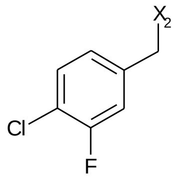
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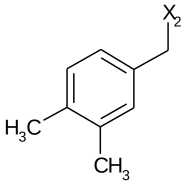
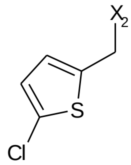
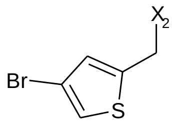
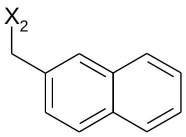
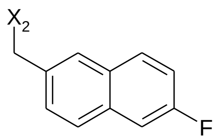
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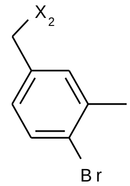
;

R^2 is selected from

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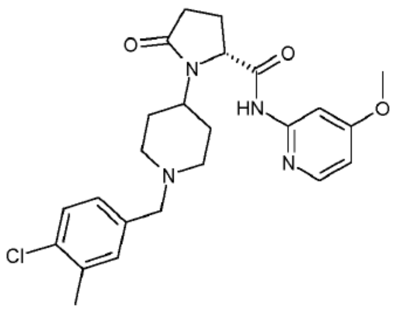
 ;

R³ is H;

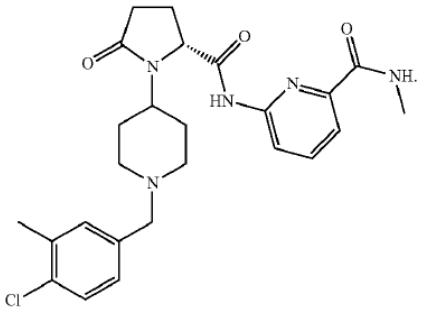
R⁴ is H;

or **R³** and **R⁴** together are forming a CH_2-CH_2 group.

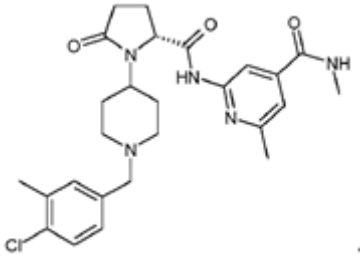
8. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



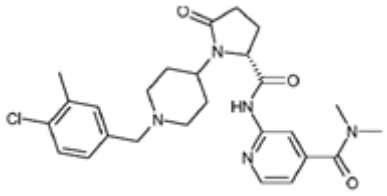
9. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



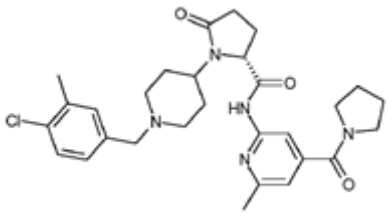
10. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



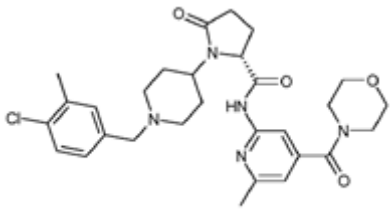
11. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



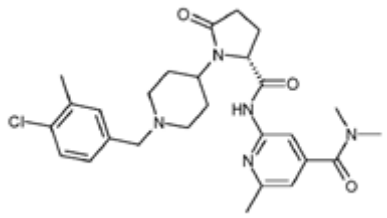
12. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



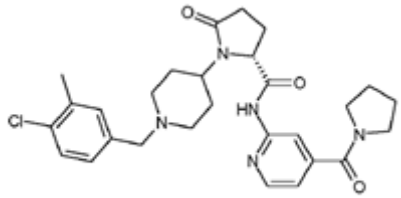
13. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



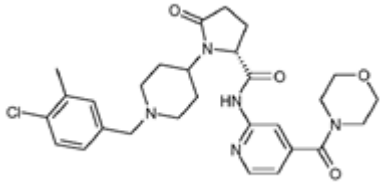
14. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



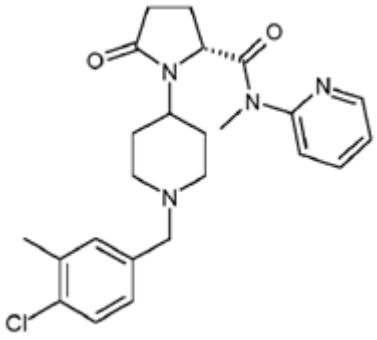
15. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



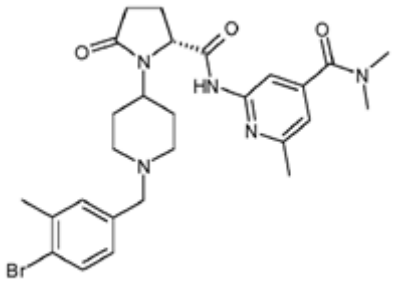
16. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



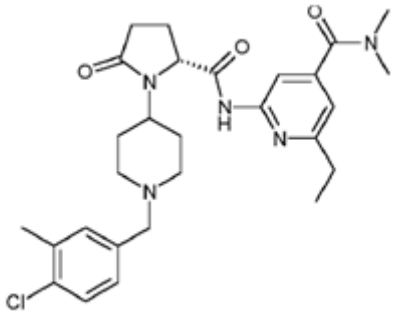
17. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



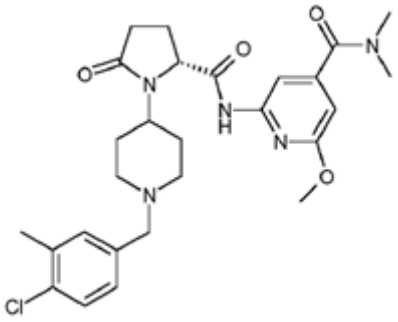
18. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



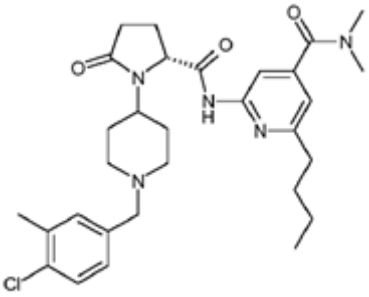
19. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



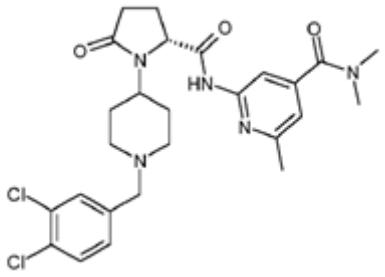
20. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



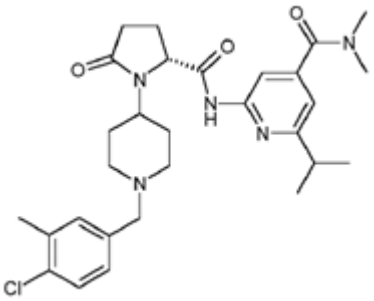
21. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



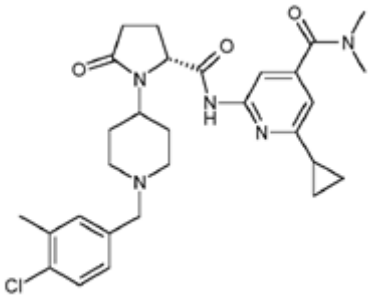
22. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



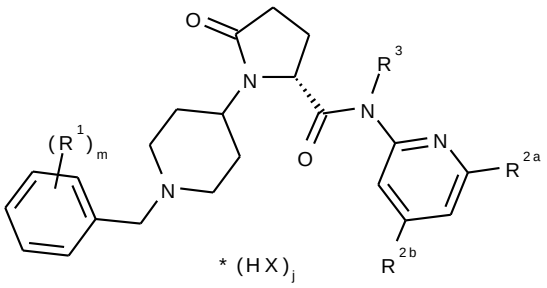
23. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



24. The use of claim 1 or 2, wherein the compound of formula 1 to be administered is



25. The use of claim 1 or 2, wherein the compound is a co-crystal of formula



wherein

R^1 is C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-haloalkyl, halogen;

m is 1, 2 or 3;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, $CONR^{2b.1}R^{2b.2}$, or halogen;

$R^{2b.1}$ is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-6}-haloalkyl;

$R^{2b.2}$ is H, or C_{1-6}-alkyl;

or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom

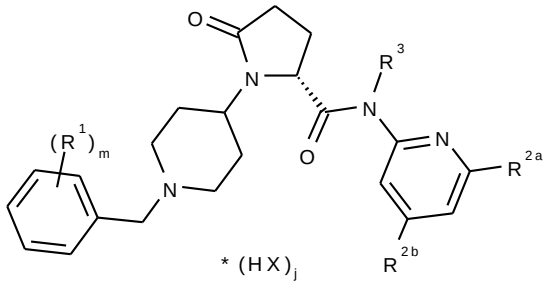
R^3 is H, or C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, benzoate, citrate, salicylate, fumarate, tartrate, dibenzoyltartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

j is 0, 0.5, 1, 1.5 or 2;

with a co-crystal former selected from the group consisting of orotic acid, hippuric acid, L-pyroglutamic acid, D-pyroglutamic acid, nicotinic acid, L-(+)-ascorbic acid, saccharin, piperazine, 3-hydroxy-2-naphtoic acid, mucic (galactaric) acid, pamoic (embonic) acid, stearic acid, cholic acid, deoxycholic acid, nicotinamide, isonicotinamide, succinamide, uracil, L-lysine, L-proline, D-valine, L-arginine, glycine.

26. The use of claim 1 or 2, wherein the compound is a co-crystal of formula



R^{2a} is H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, or $CONR^{2a.1}R^{2a.2}$;

$R^{2a.1}$ is H, C_{1-6}-alkyl, or C_{1-6}-haloalkyl;

$R^{2a.2}$ is H, or C_{1-6}-alkyl;

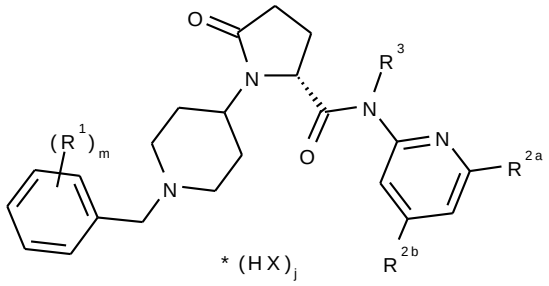
R^{2b} is H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, $CONR^{2b.1}R^{2b.2}$, or halogen;

$R^{2b.1}$ is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-6}-haloalkyl;

$R^{2b.2}$ is H, or C_{1-6}-alkyl;

or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom.

27. The use of claim 1 or 2, wherein the compound is a co-crystal of formula



R^1 is C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-haloalkyl, or halogen;

m is 1 or 2;

R^{2a} is H, or C_{1-4}-alkyl;

R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{1-4}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-4}-haloalkyl;

$R^{2b.2}$ is H, or C_{1-4}-alkyl;

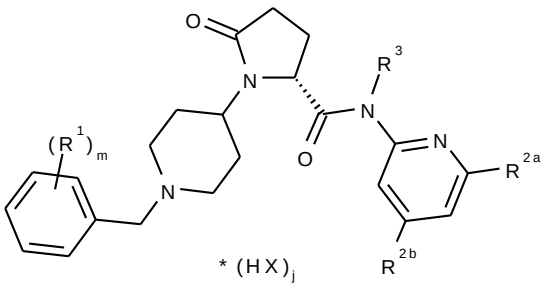
or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom

R^3 is H, or C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride or dibenzoyltartrate, and

j is 1 or 2.

28. The use of claim 1 or 2, wherein the compound is a co-crystal of formula



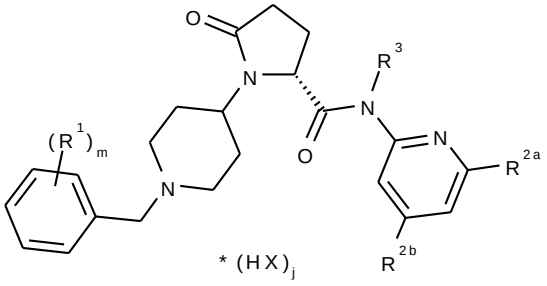
R^{2a} is H, or C_{1-4}-alkyl;

R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{1-4}-alkyl;

$R^{2b.2}$ is C_{1-4}-alkyl.

29. The use of claim 1 or 2, wherein the compound is a co-crystal of formula



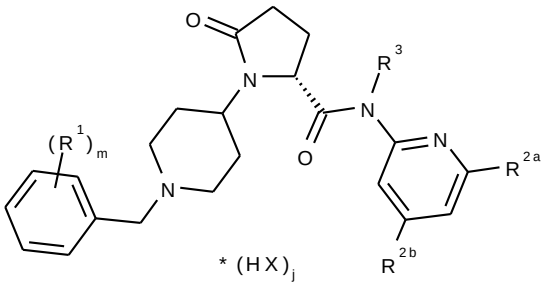
R^{2a} is H, or C_{1-4}-alkyl;

R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{0-4}-alkyl-C_{3-6}-cycloalkyl;

$R^{2b.2}$ is H, or C_{1-4}-alkyl.

30. The use of claim 1 or 2, wherein the compound is a co-crystal of formula



R^{2a} is H, or C_{1-4}-alkyl;

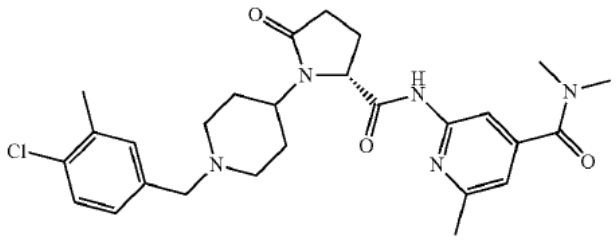
R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{1-4}-haloalkyl;

$R^{2b.2}$ is H, C_{1-4}-alkyl.

31. The use of claim 1 or 2, wherein the compound is a co-crystal of the formula according to claim 25, wherein $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom.

32. The use of claim 1 or 2, wherein the compound is a co-crystal having the formula shown below,

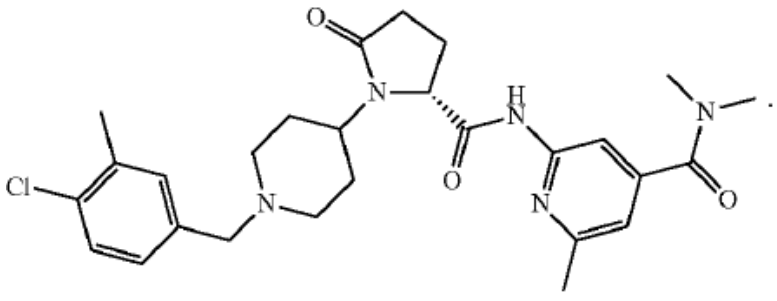


$*(HX)_j$

wherein j is 0,

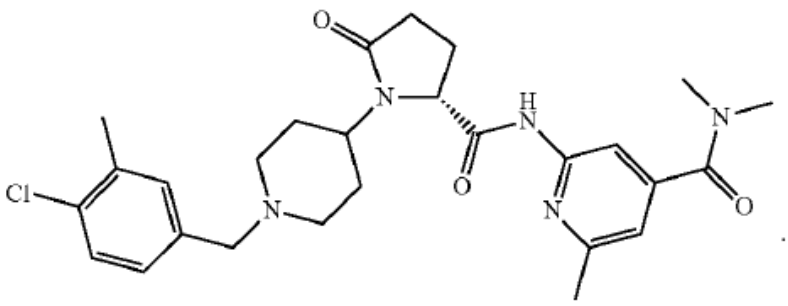
and the co-crystal former is selected from the group consisting of L-(+)-ascorbic acid, mucic acid, pamoic acid, nicotinic acid, succinamide, nicotinamide, isonicotinamide, L-lysine, and L-proline.

33. The use of claim 1 or 2, wherein the compound is a crystalline salt of the formula below,



*dibenzoyltartrate

34. The use of claim 1 or 2, wherein the compound is a crystalline salt of the formula below,



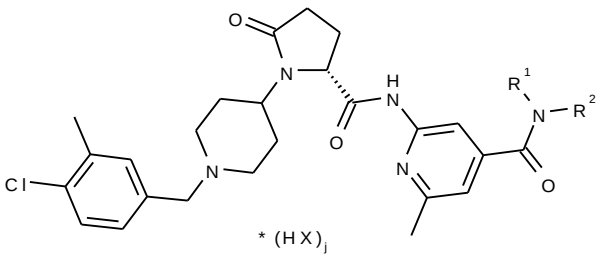
35. The use of claim 33, wherein the crystalline salt is characterized in that the four highest X-ray powder diffraction peaks occur at 3.72, 13.60, 16.89, and 19.34 degrees 2Θ (±0.05 degrees 2Θ) when measured using CuKα radiation.

36. The use of claim 34, wherein the crystalline salt is characterized in that the four highest X-ray powder diffraction peaks occur at 16.02, 16.86, 19,45, and 19.71 degrees 2Θ (±0.05 degrees 2Θ) when measured using CuKα radiation.

37. The use of claim 1 or 2, wherein the compound comprises at least one co-crystal of a compound of the formula according to claim 25 and a pharmaceutically acceptable carrier.

38. The use of claim 1 or 2, wherein the compound of formula 1 is to be administered in the form of the individual optical isomers, a mixture of the individual enantiomers, a racemate or in the form of the enantiomerically pure compounds.

39. The use of claim 1 or 2, wherein the compound is a pharmaceutical composition comprising as an active ingredient one or more compounds of the formula below,



1

wherein

R^1 is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-6}-haloalkyl;

R^2 is H, or C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride or ½ dibenzoyltartrate; and

j is 1 or 2, and

a first diluent, a second diluent, a binder, a disintegrant and a lubricant.

40. The use of claim 39 wherein the pharmaceutical composition is characterized in that

R^1 is H, or Methyl;

R^2 is H, or Methyl;

X is an anion selected from the group consisting of chloride or ½ dibenzoyltartrate; and

j is 1 or 2

41. The use of claim 39, wherein the pharmaceutical composition is characterized in that X is chloride and j is 2.

42. The use of claim 39, 40, or 41, wherein the pharmaceutical composition further comprises an additional disintegrant.

43. The use of claim 39, 40, or 41, wherein the pharmaceutical composition further comprises an additional glidant.

44. The use of claim 39, 40, or 41, wherein the diluent of the pharmaceutical composition further comprises cellulose powder, dibasic calcium phosphatae anhydrous, dibasic calcium phosphate dehydrate, erythritol, low substituted hydroxypropyl cellulose, mannitol, pregelantinized starch, or xylitol.

45. The use of claim 39, 40, or 41, wherein the lubricant of the pharmaceutical composition is talc, polyethyleneglycol, calcium behenate, calcium stearate, hydrogenated castor oil or magnesium stearate.

46. The use of claim 39, 40, or 41, wherein the binder of the pharmaceutical composition is copovidone (copolymerisates of vinylpyrrolidon with other vinylderivates),

hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC) or polyvinylpyrrolidon (Povidone).

47. The use of claim 39, 40, 41, 42, 43, 44, 45, or 46, wherein the disintegrant of the pharmaceutical composition according to claim is corn starch.

48. The use of claim 39, 40, 41, 42, 43, 44, 45, 46, or 47, wherein the optional glidant of the pharmaceutical composition is colloidal silicon dioxide.

49. The use of claim 39, wherein the pharmaceutical composition further comprises

10-90 %	active ingredient
5-70 %	diluent 1,
5-30 %	diluent 2,
0-30 %	binder,
1-12 %	disintegrant, and
0.1-3 %	lubricant.

50. The use of claim 39, wherein the pharmaceutical composition further comprises

30-70 %	active ingredient
20-75 %	diluent 1,
5-30 %	diluent 2,
2-30 %	binder,
0,5-20 %	buffering agent,
1-12 %	disintegrant, and
0.1-3 %	lubricant.

51. The use of claim 42, wherein the additional disintegrant of the pharmaceutical composition is crospovidone.

52. The use of claim 39, wherein the pharmaceutical composition is in the dosage form of a capsule, a tablet, or a film-coated tablet.

53. The use of claim 52, wherein the pharmaceutical composition further comprises a 2-4% film coat.

54. The use of claim 53, wherein the film coat comprises a film-forming agent, a plasticizer, a glidant, and optionally one or more pigments.

55. The use of claim 54, wherein the film coat comprises Polyvinyl alcohol (PVA) or hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG), talc, titanium dioxide and iron oxide.

56. The use of any of the preceding claims, further comprising that a therapeutically effective amount of an anti-VEGF therapy is to be administered.